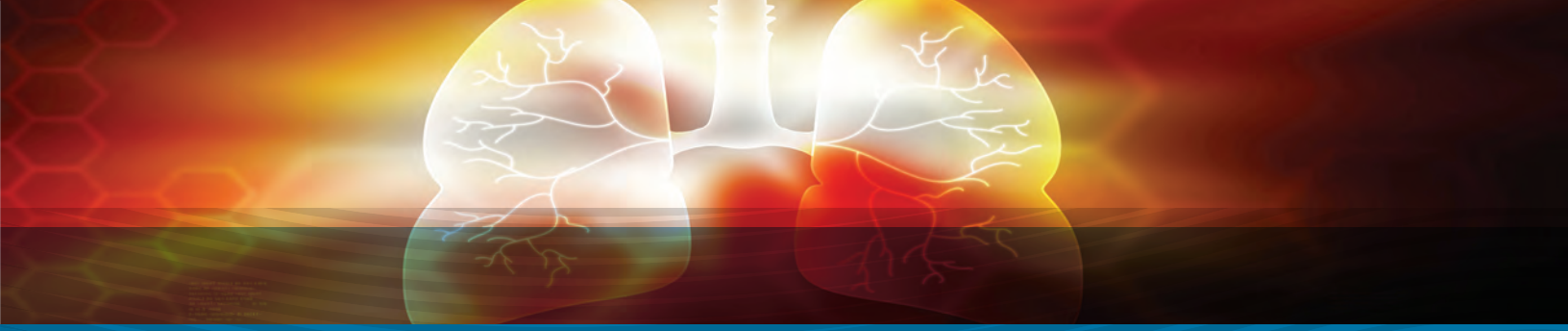

FDA Qualification of Plasma Fibrinogen as a Biomarker for Clinical Trials of Chronic Obstructive Pulmonary Disease

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Introduction

In 2004, the U.S. Food and Drug Administration (FDA) published a report titled "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to Medical Products," which concluded that significant improvements should be made to the drug development process.[1] The creation of drug development tools (methods, materials, or measures, including biomarkers) is an important component of that process. The FDA's Biomarker Qualification Program was designed to support the development of biomarkers as a drug development tool, and a guidance document was issued to support external stakeholders in this effort.[2]

The Chronic Obstructive Pulmonary Disease (COPD) Foundation Biomarker Qualification Consortium (CBQC) was formed in 2010 as a partnership between the COPD Foundation, pharmaceutical companies, academic experts, patient care groups, and the FDA. One candidate biomarker selected by the CBQC was plasma fibrinogen, a marker of systemic inflammation that is elevated in conditions such as COPD. Systemic inflammation is associated with many of the pulmonary and extra-pulmonary manifestations of COPD, although evidence indicates that not all patients with COPD have elevated concentrations of biomarkers of systemic inflammation. Research also shows that elevated levels of biomarkers such as fibrinogen are associated with a greater risk of adverse COPD outcomes including COPD exacerbations and all-cause mortality.[3-5]

In a Letter of Intent, the CBQC proposed plasma fibrinogen for two contexts of use in drug development: (1) as an enrichment factor for COPD subjects more likely to experience a COPD exacerbation, and (2) as an enrichment factor for COPD subjects at higher risk for all-cause mortality. These proposed contexts of use reflect the belief that routine assessment of fibrinogen levels in the course of the enrollment of a clinical trial may improve the identification of subjects more likely to experience COPD exacerbations or those who have a higher mortality risk. This enrichment of clinical trial populations with patients who are more likely to experience the outcome of interest during the study period would reduce the number of subjects who need to be enrolled while maintaining statistical power, and decrease both the cost and duration of the trial (due to shorter study enrollment periods).

Methods

A literature review identified potential data sources that contained measurements of fibrinogen and lung function, had available subject-level data on at least 50 patients with COPD, and had outcomes of interest (COPD

exacerbations and all-cause mortality) over a minimum of 6 months of follow-up. The following five data sources met all criteria and were obtained by the CBQC:

- The National Health and Nutrition Examination Survey III (NHANES III)[6]
- Framingham Heart Study (FHS) Offspring Cohort[7]
- Cardiovascular Health Study (CHS)[8]
- Atherosclerosis Risk in Communities Study (ARIC)[9]
- Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE)[10]

The data were compiled into an integrated dataset by INC Research, and the CBQC partnered with Evidera to assist in the development of a statistical analysis plan (SAP), conduct analyses to support the proposed contexts of use, and prepare the qualification package for submission to the FDA.

Patients aged 40+ who met the GOLD criteria for moderate, severe, or very severe COPD were eligible for inclusion.[11] Prior COPD exacerbation history was available only for patients in the ECLIPSE dataset. Outcomes of interest were moderate and hospitalized COPD exacerbations within 12 months and all-cause mortality within 36 months, and these time periods were chosen to simulate those used in a clinical trial. Fibrinogen was assessed using four hypothetical thresholds: 250 mg/dL, 300 mg/dL, 350 mg/dL, and 400 mg/dL.

"…enrichment of clinical trial populations with patients who are more likely to experience the outcome of interest during the study period would reduce the number of subjects who need to be enrolled while maintaining statistical power…"

Statistical Analyses

The demographic and clinical characteristics of patients in the integrated dataset (i.e., all five databases combined) as well as in each individual dataset were assessed using descriptive statistics. Kaplan-Meier curves were used to present time-to-event data, with some stratified by history of exacerbations (for analyses conducted using only

Table 1: Baseline Characteristics of COPD Patients

	Total (n=6,376)	ARIC (n=1,789)	CHS (n=1,292)	ECLIPSE (n=2,118)	FHS (n=145)	NHANES (n=1,032)
AGE						
Mean (SD)	63.6 (9.8)	56.5 (5.4)	73.3 (5.4)	63.4 (7.1)	46.3 (5.0)	66.5 (11.7)
Median (range)	63.0 (40.0-90.0)	57.0 (45.0–64.0)	71.5 (65.5–88.0)	64.0 (40.0–76.0)	46.0 (40.0–60.0)	67.0 (40.0–90.0)
GENDER						
Male	3929 (61.6%)	1096 (61.3%)	773 (59.8%)	1384 (65.3%)	83 (57.2%)	593 (57.5%)
RACE						
Non-white	716 (11.2%)	371 (20.7%)	65 (5.0%)	49 (2.3%)	0 (0.0%)	231 (22.4%)
White	5515 (86.5%)	1418 (79.3%)	1227 (95.0%)	2069 (97.7%)	0 (0.0%)	801 (77.6%)
Missing	145 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	145 (100.0%)	0 (0.0%)
ETHNICITY						
Hispanic or Latino	262 (4.1%)	0 (0.0%)	9 (0.7%)	101 (4.8%)	0 (0.0%)	152 (14.7%)
Not Hispanic or Latino	4176 (65.5%)	0 (0.0%)	1279 (99.0%)	2017 (95.2%)	0 (0.0%)	880 (85.3%)
Missing	1938 (30.4%)	1789 (100.0%)	4 (0.3%)	0 (0.0%)	145 (100.0%)	0 (0.0%)
SMOKING STATUS						
Never	787 (12.3%)	229 (12.8%)	289 (22.4%)	0 (0.0%)	30 (20.7%)	239 (23.2%)
Former Smoker	3010 (47.2%)	534 (29.8%)	701 (54.3%)	1350 (63.7%)	31 (21.4%)	394 (38.2%)
Current Smoker	2579 (40.4%)	1026 (57.4%)	302 (23.4%)	768 (36.3%)	84 (57.9%)	399 (38.7%)
FIBRINOGEN LEVELS						
Mean Fibrinogen (SD)	351.7 (89.3)	322.2 (74.3)	328.6 (68.4)	397.3 (91.9)	334.6 (68.3)	340.8 (96.3)

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Figure 1: Time to First COPD Exacerbation Within 12 Months, ECLIPSE: Fibrinogen Threshold 350 mg/dL

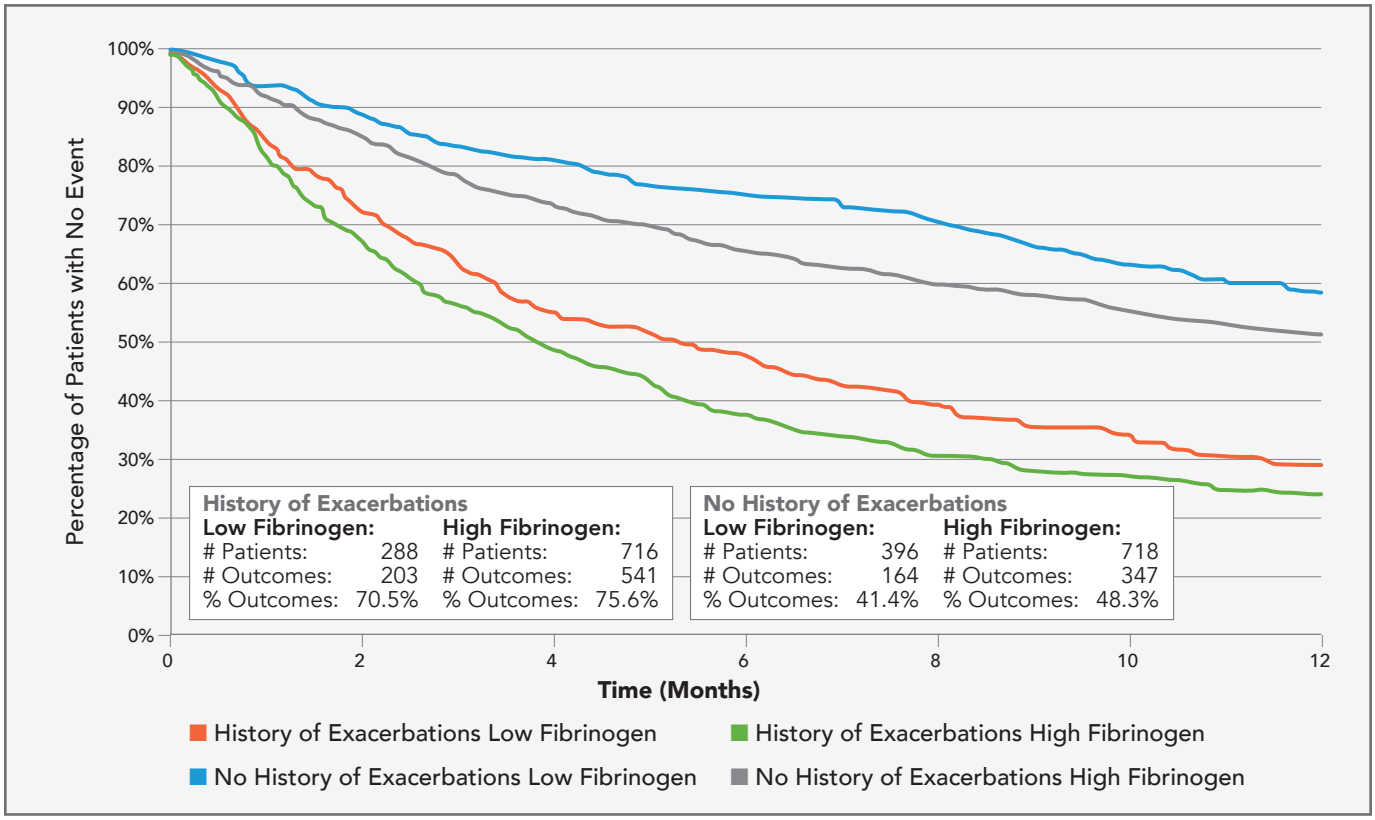

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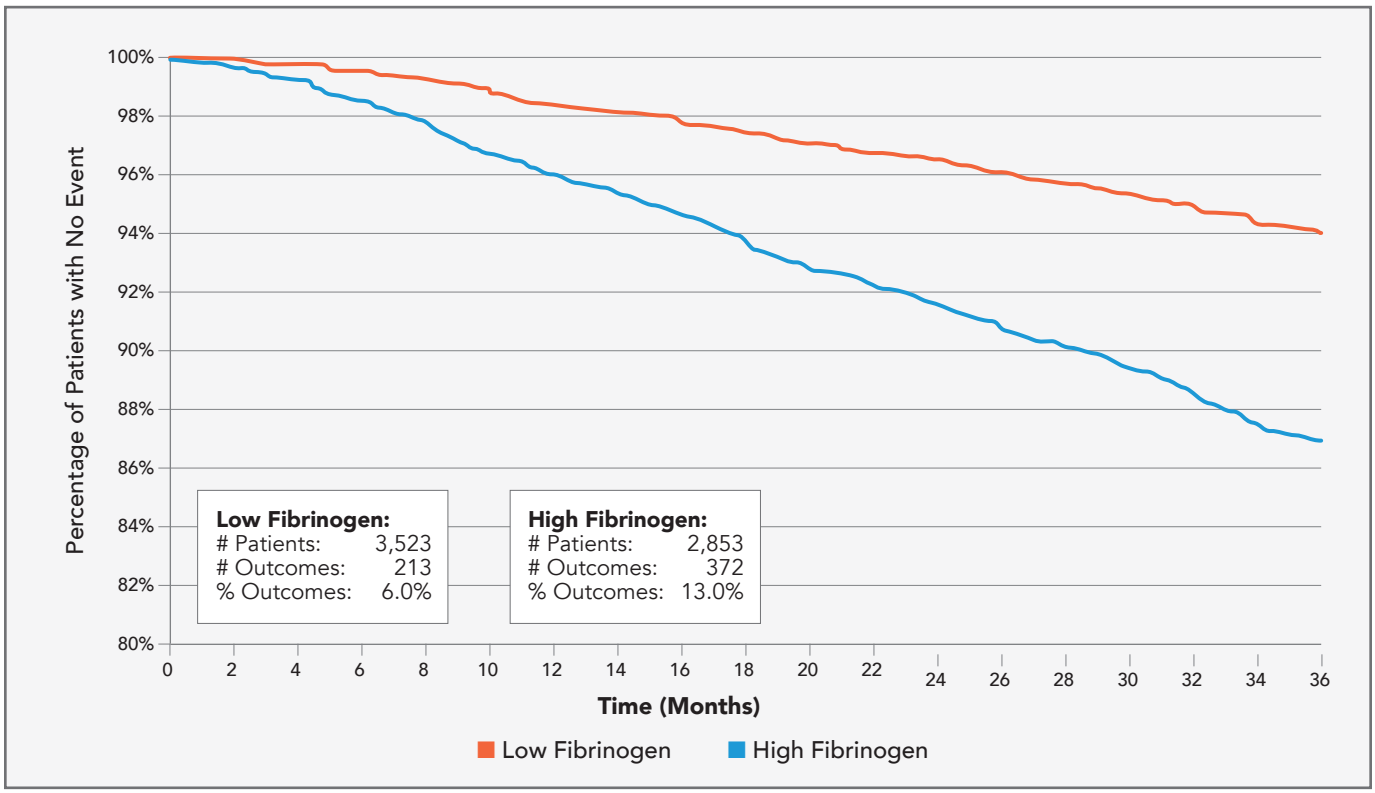
Figure 2: Time to Death Within 36 months, All Patients: Fibrinogen Threshold 350 mg/dL



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data from ECLIPSE). Univariate analyses were performed to assess the relationship between clinically relevant covariates and the outcomes of interest. Multivariable Cox proportional hazards models were used to present the association between fibrinogen and COPD outcomes after adjusting for relevant covariates. Finally, analyses were conducted to compare the sample sizes required in hypothetical clinical trials with and without the use of a fibrinogen threshold as part of the inclusion criteria. Confidence intervals presented in these sample size analyses were obtained using bootstrapping procedures.

"These analyses provide evidence from a range of heterogenous longitudinal datasets that elevated levels of fibrinogen among subjects with COPD are associated with outcomes commonly used as endpoints in clinical trials…"

Selected Results

A total of 6,376 patients from ARIC, CHS, ECLIPSE, FHS, and NHANES met the inclusion criteria for analyses. The mean age of patients was 63.6 ± 9.8 years (Table 1), the majority (61.9%) were male, and most were either former (47.2%) or current smokers (40.4%). The pooled mean baseline fibrinogen level was 351.7 ± 89.3 mg/dL among COPD participants included in the integrated dataset.

The time to any exacerbation (moderate or hospitalized exacerbation) within 12 months among patients in ECLIPSE is presented in Figure 1. Using a threshold of 350 mg/dL (i.e., "high" is equivalent to fibrinogen levels ≥ 350 mg/dL), 41.4% of individuals with low fibrinogen had an exacerbation within 12 months, compared to 48.3% with high fibrinogen. ECLIPSE subjects with a history of 1 or more COPD exacerbations and high fibrinogen were at higher risk for another exacerbation of any type within 12 months when compared to participants with a history of exacerbations and low fibrinogen (75.6% vs. 70.5%).

Using the same threshold, 6.0% of participants with low fibrinogen in ARIC, CHS, ECLIPSE, FHS, and NHANES had died within 36 months, compared to 13.0% of participants with high fibrinogen (Figure 2). High fibrinogen was associated with an increased risk of death within 36 months (HR: 1.94; 95% CI: 1.62–2.31) among all participants.

Table 2: Sample sizes (95% CI) by fibrinogen levels and hazard ratios based on the number of hospitalized exacerbations over a 12-month time-period for ECLIPSE subjects by history of exacerbation

Fibrinogen Level	Total N	N (%) of Subjects with Hospitalized Exacerbation within 12 Months	Total Sample Size by Hazard Ratio			
			HR=0.70	Difference Over No Threshold, n (%)	HR=0.80	Difference Over No Threshold, n (%)
Without a History of Exacerbation						
No Threshold	1,114	94 (8%)	4,528 (3,590-5,580)		10,808 (8,574-13,316)	
> 250	1,082	94 (9%)	4,418 (3,476-5,384)	-110 (-2%)	10,546 (8,304-12,850)	-262 (-2%)
> 300	973	87 (9%)	4,348 (3,474-5,318)	-180 (-4%)	10,382 (8,300-12,690)	-426 (-4%)
> 350	718	70 (10%)	4,078 (3,144-5,266)	-450 (-10%)	9,738 (7,514-12,568)	-1,070 (-10%)
> 400	441	49 (11%)	3,806 (2,782-5,088)	-722 (-16%)	9,088 (6,652-12,146)	-1,720 (-16%)
With History of Exacerbation						
No Threshold	1,004	241 (24%)	1,338 (1,198-1,490)		3,212 (2,878-3,572)	
> 250	985	239 (24%)	1,328 (1,202-1,458)	-10 (-1%)	3,186 (2,888-3,500)	-26 (1%)
> 300	901	230 (26%)	1,268 (1,142-1,402)	-70 (-5%)	3,044 (2,746-3,366)	-168 (-5%)
> 350	716	199 (28%)	1,182 (1,058-1,346)	-156 (-12%)	2,840 (2,546-2,230)	-372 (-12%)
> 400	488	149 (31%)	1,090 (954-1,248)	-248 (-19%)	2,620 (2,296-2,998)	-592 (-18%)

Table 3: Sample sizes (95% CI) by fibrinogen levels and hazard ratios based on the number of deaths over a 3-year time-period for ECLIPSE subjects by history of exacerbation

Fibrinogen Level	N	N (%) of Subjects with Mortality within 36 Months	Total Sample Size by Hazard Ratio			
			HR=0.70	Difference Over No Threshold, n (%)	HR=0.80	Difference Over No Threshold, n (%)
Without a History of Exacerbation						
No Threshold	1,114	32 (3%)	4,744 (3,836-6,116)		11,398 (9,164-14,956)	
> 250	1,082	30 (3%)	4,862 (3,806-6,364)	+118 (2%)	11,606 (9,094-15,188)	+208 (2%)
> 300	973	28 (3%)	4,888 (3,986-6,512)	+144 (3%)	11,670 (9,520-15,540)	+272 (2%)
> 350	718	27 (4%)	4,090 (3,254-5,384)	-654 (-14%)	9,766 (7,778-12,852)	-1,632 (-14%)
> 400	441	20 (5%)	3,790 (2,906-5,172)	-954 (-20%)	9,052 (6,948-12,344)	-2,346 (-21%)
With History of Exacerbation						
No Threshold	1,004	37 (4%)	3,830 (3,024-4,640)		9,146 (7,228-11,078)	
> 250	985	35 (4%)	3,926 (3,206-4,868)	+96 (3%)	9,380 (7,662-11,622)	+234 (3%)
> 300	901	34 (4%)	3,732 (2,948-4,568)	-98 (-3%)	8,916 (7,050-10,908)	-230 (-3%)
> 350	716	28 (4%)	3,536 (2,782-4,414)	-294 (-8%)	8,446 (6,652-10,540)	-700 (-8%)
> 400	488	24 (5%)	3,062 (2,374-3,916)	-768 (-20%)	7,318 (5,684-9,356)	-1,828 (-20%)

Table 2 presents the difference in sample size required for a clinical trial with hospitalized exacerbations within 12 months as an outcome when a fibrinogen threshold is applied. For example, at a hazard ratio of 0.70, the sample size of each arm (treatment and control) among patients who had at least one previous exacerbation could be reduced by 5% using a threshold of 300 mg/dL, by 12% using a threshold of 350 mg/dL, and by 19% using a threshold of 400 mg/dL. Likewise, the sample size of each arm in a trial of mortality within 36 months and hazard ratio of 0.70 (Table 3) could be reduced by 3% using a threshold of 300 mg/dL, 8% using a threshold of 350 mg/dL, and 20% using a threshold of 400 mg/dL, among patients with a history of at least one COPD exacerbation.

Conclusion

These analyses provide evidence from a range of heterogenous longitudinal datasets that elevated levels of fibrinogen among subjects with COPD are associated with outcomes commonly used as endpoints in clinical trials, including COPD exacerbations within one year and death within three years. Data from the ECLIPSE study indicate that this relationship also holds among the subset of patients who have a history of exacerbations, and these patients typically form the subject pool for COPD clinical trials assessing the impact of an intervention on COPD exacerbations. Further analyses indicate that the use of a fibrinogen threshold during the enrollment phase of a clinical trial would permit a reduction in the sample size of each study arm, while maintaining the statistical power of that trial.

On July 6, 2015, the FDA qualified plasma fibrinogen as a prognostic biomarker for enrichment of clinical trials in COPD.[12] This qualification permits the use of fibrinogen for clinical trial enrichment in submissions for investigational new drug applications, new drug applications, and biologics license applications without additional review from the FDA to reconfirm the suitability of fibrinogen as a biomarker. The successful qualification of plasma fibrinogen as a prognostic biomarker for use in COPD drug development is an important step in the effort to facilitate clinical trials of novel therapies and demonstrates the value of a public-private consortium working with regulatory officials.

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